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6 PULMONARY ADAPTATION TO HIGH ALTITUDE.

9 ANNUAL SUMMARY REPORT, 1 Feb - 18 Nov 77

10 Jerome A. Dempsey Ph.D.

11 18 Nov ~~1977~~ 1977

12 8 p.

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Washington, D.C. 20314

15
new Contract No. DAMD 17-77-c-7006

University of Wisconsin
Madison, Wisconsin 53706

16 3E161102 B548 17 40

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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Pulmonary Adaptation to High Altitude		5. TYPE OF REPORT & PERIOD COVERED Annual Summary Report (2/1/77 to 11/18/77)
		6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) Jerome A. Dempsey, Ph.D.		8. CONTRACT OR GRANT NUMBER(s) DAMD-17-77-C-7006 ^{new}
9. PERFORMING ORGANIZATION NAME AND ADDRESS Jerome A. Dempsey, Ph.D. University of Wisconsin ✓ 504 N. Walnut St., Madison, WI 53706		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 61102A 3E161102BS08.00.021
11. CONTROLLING OFFICE NAME AND ADDRESS US Army Medical Research and Development Command, Washington, DC 20314		12. REPORT DATE 11/18/77
		13. NUMBER OF PAGES 9 pages
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		15. SECURITY CLASS. (of this report) Unclassified
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE
16. DISTRIBUTION STATEMENT (of this Report) Approved for Public Release, Distribution Unlimited		
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)		
18. SUPPLEMENTARY NOTES		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) High altitude, control of breathing, brain metabolism, cerebrospinal fluid, brain acid-base status, cerebral hypoxia. ICF/ECF		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) This project is aimed at two closely related questions concerning man's adaptation to high altitude hypoxia: (1) What mechanisms regulate the ionic composition of brain intra- and extra-cellular fluid in long-term hypoxia? and (2) What role do these regulatory factors play in mediating ventilatory acclimatization to hypoxia? In the first 9 months of our contract we have accomplished the following in pursuit of these goals. First, in studies of brain ECF in hypoxia we have determined the regulation of CSF [HCO ₃] ⁻ movement (CONTINUED...)		

20. ABSTRACT (Continued)

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between plasma and CSF, described the effects of hypoxia on brain PCO_2 gradients, described the ventilatory response of the awake rat to steady-state ventricular-cisternal perfusion of various (H^+) , and--in man--^{has} shown that the time-course of ventilatory "de-acclimatization" from chronic hypoxia is not explained by changes in CSF (H^+) . Secondly, we have developed techniques ^{he has} for the study of brain intra-cellular pH and cerebral metabolism in dogs, and begun the collection of data in control and short-term hypoxic conditions. Thirdly, ^{he} we are well underway in ^{our} studies of brain neurotransmitters in hypoxia. That is, assays have been developed, control data has been obtained in many rats, the time-course of ventilatory acclimatization to chronic hypoxia in the awake rat has been described and we have ^{he has} completed initial studies of the affect of specific neurotransmitter blockade on the control of breathing in the awake animal. In summary, our goal for the first year of this contract was primarily aimed at establishing specific methods and techniques. This has been accomplished and we are well underway in our application of these techniques to the principal physiological questions.

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ANNUAL PROGRESS REPORT

Our application for an Army contract in the fall of 1976 outlined our general and specific aims as those which we felt could be accomplished over a two year period. During this initial nine months of the contract (February through November 1977) we feel our progress has been adequate and that we can reaffirm our original estimate that our aims will be accomplished in the stipulated two year period.

General and Specific Aims

The proposed studies are aimed at two closely related questions. Namely; 1) What mechanisms dominate the regulation of the ionic environment of brain intra- and extra-cellular fluids during chronic hypoxia and hypocapnia? and 2) What role do these regulatory processes play in explaining man's acclimatization to chronic hypoxia? Factors of major interest in the acclimatization process at high altitude were ventilatory and acute mountain sickness.

Specifically, we have undertaken four types of studies in pursuit of these aims, all concerned with the effects of hypoxic exposure:

1. Brain extra-cellular fluid (ECF) regulation and its role in ventilatory acclimatization.
2. Regulation of brain intra-cellular $[H^+]$ and metabolism.
3. Role of brain neurotransmitters in acclimatization.
4. Effects of carbonic anhydrase inhibition on brain intra- and extra-cellular fluid and neurotransmitters.

PROGRESS TO DATE

I. Brain Extra-cellular Fluid - Its Regulation and Role in Control of Breathing.

Our specific goals here were to continue our work on CSF $[HCO_3^-]$ regulation in dogs, to determine the role of CSF $[H^+]$ in ventilatory de-acclimatization from hypoxia in man and to determine the role of any factors in the ionic composition of brain ECF which might influence ventilatory acclimatization to hypoxia.

- A. CSF $[HCO_3^-]$ regulation in dogs during hypocapnia. This study is now completed, and has shown the following: (1) hypocapnia causes an increased movement of bicarbonate from plasma to CSF (and vice versa); (2) this increased flux is not secondary to a general "permeability" change in the blood-brain barrier as shown by our finding that movement of labeled sulphate into the CSF is not altered by hypocapnia; (3) from our studies of labeled Na and Cl^- , we conclude that the increased movement of HCO_3^- between CSF and blood in hypocapnia is produced by an enhanced movement of Na and a substantially retarded movement of Cl^- into CSF. These data explain the underlying mechanisms regulating those CSF $[HCO_3^-]$ and $[H^+]$ changes which we have previously documented in man during sojourn at high altitudes.

- B. Regulation of PCO_2 gradients in dog brain. This data has a technical base in that it permitted us to determine the effects of hypocapnia and hypoxia on PCO_2 differences between cerebral venous and arterial blood and CSF. The study was completed in the first two months of the current contract and was published in the September issue of J. of Appl. Physiology. The relevant conclusion here is that we must measure and know the actual CSF PCO_2 in dog brain to have a valid estimate of brain tissue PCO_2 for our intra-cellular pH studies. Previous suggestions of obtaining this value from a knowledge of arterial and cerebral venous PCO_2 are not valid under conditions of hypoxic hypocapnia which occurs in man and animals at high altitudes.
- C. Role of CSF $[H^+]$ in ventilatory de-acclimatization in man. This study was conducted from May to August of 1977 and is now completed. This continuing question was once again tested by examining the relationship of CSF $[H^+]$ in man (lumbar) and pony (cisternal) to ventilation during 24 hours of "de-acclimatization" from 4300 m. The recent claim by Severinghaus, et al. is that CSF pH moves 0.005 units acid to normal after 1 hour return to normoxia and is therefore sufficient to drive the residual hyperventilation during this period. We examined a much longer time-course and found the following in both pony (n=6) and man (n=7): (1) following 3-5 days at 4300 m, ventilation and arterial acid-base status returns to normal sea-level values after 24 hours in normoxia; (2) after 1 hour return to normoxia, CSF $[H^+]$ was equal to or perhaps even $\sim .01$ acid to sea-level normal in some subjects, i.e. we agree with the Severinghaus data; and (3) with further duration of normoxia ("de-acclimatization") as ventilation decreased and $PaCO_2$ rose, CSF pH became more acid. Clearly CSF $[H^+]$ was a function of ventilation in this physiologic situation--a conclusion which fits with all of our previous data on this topic. We believe these data really cast the most serious of doubts on the whole concept of brain ECF $[H^+]$ as a critical mediator of ventilation in man--in hypoxic or normoxic conditions.
- D. Factors in brain ECF in the (awake, unrestrained) rat. Perfusion of the brain is an extremely difficult procedure in the awake animal. We have yet to do the crucial experiments of "cross-perfusion" of CSF from one animal to another, i.e. we have accomplished this in 6 animals to date but with substantial technical problems. We have accomplished the following using this preparation: (1) completely described the ventilatory response to a wide range of changes in brain ECF $[H^+]$ over a time-course of minutes through 6-8 hours of perfusion in the awake rat. This was a descriptive basis necessary for further studies of perfusion in this animal; (2) tested the effects of very wide variations in ECF $[H^+]$ (induced by ventricular perfusion) on ventilatory acclimatization in the chronically hypoxic rat; and (3) developed micro-methods for acid-base analysis of brain CSF and methods for obtaining the 50-60 μl of CSF from the cistern of the acclimatized rat.

II. Brain Intra-cellular [H⁺] and Its Contribution to Ventilatory Acclimatization (Dog).

Our first year goal was method development and as of these past few weeks we are well ahead of schedule: (1) we can obtain and reproduce values for CSF and arterial blood in the awake dog; (2) we can accurately and reproducibly measure brain extra-cellular fluid volume and intra-cellular [H⁺] ([H⁺]_i) in various regions of dog brain. The two methods of [H⁺]_i agree quite well; and (3) our fluorometric assays of metabolites in brain tissue have progressed well. All methods for these assays are now completed and we have only a few weeks of work left for careful checking of reproducibility of our assay techniques. We have thus far applied this technique to several "control" animals (in normoxic normocapnia) and a few animals in short-term hypoxia. The remainder of this year, then, will be devoted to further work on the validation of fluorometric assays, gathering of control data on [H⁺]_i in control animals and determining the effects of a few hours of hypoxic hypocapnia (equivalent to man at 4300 m altitude) on brain [H⁺]_i.

III. Regulation and Role of Brain Neurotransmitters in Acclimatization to High Altitudes.

These studies were aimed at delineating the role of factors other than [H⁺] in the mediation of ventilatory acclimatization with specific emphasis on contribution from supra-portine areas; and also at the question of cerebral hypoxia in acute mountain sickness (see IV below).

We have accomplished the following to date in this area of research: (1) assays for brain neurotransmitter levels and turnover have been developed and their validity and reproducibility assessed. Normal "control" values have been established in over 50 animals; (2) techniques have been developed and tested for study of ventilation, metabolic rate and blood gases in the awake unrestrained rat. Further, we have detailed the time-course of changes in these variables over the duration of exposure to chronic hypoxia. The rat has shown to be a very good and perhaps even unique animal model for the study of human ventilatory acclimatization. (These studies are completed and have been submitted for publication); and (3) we are well into studies of the effect of specific neurotransmitter block agents on the control of breathing. Thus far, blockade of serotonin--especially its turnover rate--has shown powerful and sustained effects on ventilation (i.e. a persistent hyperventilation and respiratory alkalosis is produced).

IV. How Carbonic Anhydrase Inhibition (CAI) and other Pharmacological Treatments for Acute Mountain Sickness Affect Brain Intra- and Extra-cellular Fluid Composition.

Like most of our other studies these have awaited development of specific laboratory techniques. We have tested one of our hypotheses to date (as stated in the "Supplement" to the original application) and found it untenable. That is, Diamox had no effect on CSF pressure in the normoxic or hypoxic awake rat. In fact, hypoxia, itself, was without effect on CSF pressure.

V. Publications (2/1/77-11/1/77)

A. Published

1. Pelligrino, D.A. and J.A. Dempsey. "Effects of hypocapnia on PCO_2 gradients between CSF and cerebral capillary blood." J. Appl. Physiol., 43(3):480-486, 1977.
2. Dempsey, J.A., J.B. Skatrud, H.V. Forster, P.G. Hanson and L.W. Chosy. "Is brain ECF $[\text{H}^+]$ an important drive to breathe in man?" Presented before the 20th Annual Aspen Conference, Aspen, Colorado, June 1977 (Proceedings in press, Chest).
3. Dempsey, J.A. and S.M. Mastenbrook, Jr. "Blood gas homeostasis in health and disease." Symposium of the same name, Vancouver, British Columbia, Canada, April 1977 (Proceedings in press).

B. Manuscripts Completed - Submitted for Publication

1. E.B. Olson, Jr. and J.A. Dempsey. "The awake rat as a model for human ventilatory acclimatization to hypoxia." Submitted to J. Appl. Physiol.

C. Studies Completed - Manuscripts in Preparation

1. Dempsey, J.A. "CSF $[\text{H}^+]$ as a function of ventilation in man during de-acclimatization from chronic hypoxia."
2. Pelligrino, D.A. and J.A. Dempsey. " HCO_3^- , Na and Cl^- exchange between CSF and plasma during hypocapnia."
3. Aggarwal, D. and J.A. Dempsey. "Ventilatory response to brain ECF $[\text{H}^+]$ via ventricular perfusion in the awake rat."

VI. Military Significance

The proposed study is concerned with basic mechanisms which regulate man's biological adaptation to high altitudes. We believe these two studies are relevant to the biological well-being of the soldier in this environment in two broad respects.

Generally, if the basic mechanisms underlying a specific adaptation are understood then one greatly increases the capability for modifying or enhancing the specific acclimatization process. This concept seems particularly applicable to the process of ventilatory acclimatization. Ventilatory adaptation to hypoxia represents the single most vital and universal aspect of man's acclimatization process at high altitude. While this process is critical to the protection of oxygen transport at high altitude it is at the same time achieved at high physiologic cost. Indeed, during sustained exercise in the sojourner at high altitude the very high "cost" of achieving the ventilatory response may well outweigh the benefit, and the result is decreased physical performance capability. Our studies propose to investigate not only the basic mechanisms of this acclimatization process but will look specifically at factors--thermal state, blood acidity and/or state of physical training--which will modify the hyperventilatory response to prolonged work.

At a more basic level we will also investigate the brain's biochemical changes at high altitude. Specifically, the control of brain acid-base status and of brain neurotransmitter turnover will be thoroughly described and the effects of potential modifying agents will be examined. We speculate that

these changes in brain tissue and extra-cellular fluid will have effects on the control of breathing in hypoxia. More certainly, these parameters are also critical in determining the depression and recovery from depression of the central nervous system in hypoxia and hence, once again, will have a direct bearing on man's functional capability at high altitude. Many of the studies will be conducted in the rat and the question of relevance to man is certainly a critical one. We are aware of the many complications of species' differences, but at the same time wish to emphasize that our findings to date in the awake, unrestrained rat show that this animal is truly unique in the manner in which he mimics man's ventilatory acclimatization to chronic hypoxia.

The prevention of acute mountain sickness by pharmacological means is a controversial and unresolved problem. Our approach to this problem is based on the concept that these symptoms and the deterioration of CNS function at high altitudes is closely linked with cerebral hypoxia. In turn, it is known that of all biochemical parameters measurable in brain tissue, changes in neurotransmitter turnover are clearly the most susceptible to even small changes in the body's level of oxygenation. Hence, our approach of assessing various pharmacological interventions in hypoxia according to their effect on brain neurotransmitter turnover should be productive.

VII. Facilities

For the most part our research facilities have not changed from those described in the original proposal and include a fully equipped pulmonary physiology laboratory, ready access to laboratories in Colorado or hypobaric chambers in Milwaukee and adequate University computing facilities. The major addition is a hypobaric chamber facility obtained in cooperation with other scientists at the University. Extensive renovation of this chamber is about to begin and we expect to have it available for our studies by spring of 1978.

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SUPPLEMENTARY

INFORMATION

ADA 049857

Date changes

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
	AD-A049857	
4. TITLE (and Subtitle)		5. TYPE OF REPORT & PERIOD COVERED
Pulmonary Adaptation to High Altitude		Annual Summary Report (2/1/77 to 1/31/78)
		6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s)		8. CONTRACT OR GRANT NUMBER(s)
Jerome A. Dempsey, Ph.D.		DAMD-17-77-C-7006
9. PERFORMING ORGANIZATION NAME AND ADDRESS		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
Jerome A. Dempsey, Ph.D. University of Wisconsin 504 N. Walnut St., Madison, WI 53706		61102A 3E161102BS08.00.021
11. CONTROLLING OFFICE NAME AND ADDRESS		12. REPORT DATE
US Army Medical Research and Development Command, Washington, DC 20314		11/30/77 1/31/78
		13. NUMBER OF PAGES
		9 pages
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		15. SECURITY CLASS. (of this report)
		Unclassified
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE
16. DISTRIBUTION STATEMENT (of this Report)		
Approved for Public Release, Distribution Unlimited		
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